Anteriovenous concentration differences coupled with regional blood-flow rates determined that β-hydroxybutyrate and acetoacetate replace glucose as the dominant fuel for brain metabolism during fasting. (The SCW® indicates that this paper has been cited in over 520 publications.)

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June 17, 1987

Previous studies on brain metabolism showed that the only energy-yielding substrate consistently extracted from the blood by the human brain was glucose. The quantity of carbohydrate stored in the human body is limited and can supply organs dependent upon glucose for only a few days. During starvation the liver produces glucose for terminal oxidation from amino acids derived from proteolysis and from glycerol derived from lipolysis. The amount of nitrogen excreted in the urine reflects amino acid catabolism. During starvation, the kidneys excrete far less nitrogen than is required for gluconeogenesis to supply the central nervous system (CNS) with glucose as the only fuel source.

George F. Cahill, at the Elliott P. Joslin Research Laboratories, recognized the paradox between the absolute requirement of glucose for the brain and the quantity of nitrogen excreted from the body during prolonged starvation. He suggested that it was likely that fuels (ketone bodies) other than glucose were oxidized by the CNS during starvation.

Cahill is a creative, colorful man who had developed vibrant, cohesive research laboratories staffed by junior faculty, fellows, and proud, hardworking technicians who strove for exactness, and a new, accurate, and specific enzymatic technique for measuring blood concentrations of ketone bodies (acetoacetate and β-hydroxybutyrate) became available. I arrived in Boston in July 1965, while the Cahill family was on vacation. Cahill generously permitted my family to temporarily live in their home, with its serene surroundings and a richly endowed library. After returning from vacation, Cahill became my mentor, and research efforts were initiated under his tutelage. In addition, his collaborators and staff provided me with the guidance and opportunity necessary to investigate the nature and extent of fuels utilized by the brain during prolonged starvation.

After a 40- to 42-day fast, three obese volunteers underwent catheterization studies, partly to measure the exchange rates of ketone bodies, glucose, free fatty acids, amino acids, O₂, CO₂, and other substrates in blood across the brain and liver. This study showed that during prolonged starvation, β-hydroxybutyrate and acetoacetate replace glucose as the only fuel utilized by the brain. "It is an established fact that, despite the paradox between the need for brain glucose and the lack of brain glucose in prolonged starvation, the brain can and must continue to operate at the level of performance required for consciousness and homeostasis, not only during nutritional deprivation but also during diseased states of diabetic ketoacidosis and alcoholic hepatic cirrhosis. Simple mathematics and logic were used in a methodical approach to delineate the physiology of fuel homoeostasis. Regardless of why the work on brain metabolism during fasting became a Citation Classic, recognition of this report brings me joy."

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